REMARKS

Applicants respectfully request the Examiner to reconsider the present application in view of the following remarks.

Status of the Claims

Claims 13-23 are currently pending in the present application. The Office Action is non-final. Claims 16-19 and 21-23 are withdrawn from further consideration as being directed to a non-elected invention. Claims 13-15 and 20 are being examined on the merits. Since no further claim amendments are presented, no new matter has been added. Based upon the above considerations, withdrawal of all rejections is respectfully requested.

Objection to the Specification

The Examiner objected to the specification due to informalities. The Examiner indicated that the abstract was not in proper form. Applicants amended the abstract to place the abstract in proper form. Applicants respectfully request reconsideration and withdrawal of the present objection.

37 C.F.R. § 1.132 Declaration

A 37 C.F.R. § 1.132 Declaration of Dr. Brian Frøstrup, is enclosed with the instant reply. An executed Declaration will be submitted upon receipt from the Applicants.

The Examiner is respectfully requested to review Dr. Frøstrup's enclosed Declaration at this time, as it is material to a consideration of whether the below cited references renders obvious any of instantly pending claims 13-23.

Issues Under 35 U.S.C. § 103(a), Obviousness

Claims 13-15 and 20 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Scheel-Kruger *et al.*, U.S. Patent No. 6,288,079 B1, (hereinafter the "'079" patent) as evidence by Berge *et al.*, "*Pharmaceutical Salts*," J. Pharm. Sci., Vol. 66(1), pp. 1-19, (1977) (hereinafter "Berge").

The Examiner asserts that the '079 patent discloses the salt (1R, 2R, 3S, 5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane citrate (column 22, lines 5-40, example 15) and discloses the pharmaceutically acceptable addition salts including the tartrate salt as salts formed by procedures well know in the art. Additionally the Examiner asserts that the '079 patent further specifies that these compounds may exist unsolvated (meaning anhydrous) as well as in solvated forms (monohydrate, polyhydrate), and as isomers and mixtures.

The Examiner further asserts that pharmaceutical formulations comprising pharmaceutically acceptable salts or derivatives with acceptable carriers are also mentioned and that Berge describes that tartrate salts are the 4th most commonly commercially marketed salts.

Additionally, the Examiner suggests that organic salts of basic drugs, such as tartrate salts, are more soluble in water than inorganic salts and that dicarboxylate salts with small alkyl groups where the alkyl group is hydroxylated increases solubility of the drug (page 8, 1st column, 1st and 2nd paragraph).

The Examiner suggests that based on the teachings of the '079 patent, it would have been *prima facie* obvious to make the salt (1R, 2R, 3S, 5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate, the L-isomer of such octane tartrate salt, the monohydrate of such octane L-tartrate salt and a pharmaceutical composition comprising a therapeutically effective amount of the above-mentioned salt. Applicants respectfully traverse.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), has provided the controlling framework for an obviousness analysis. A proper analysis under § 103(a) requires consideration of the four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467.

M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. But before the Examiner can utilize these guidelines, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*; *supra*. To reject a claim based on the above mentioned guidelines, the Examiner must resolve the *Graham* factual inquiries. MPEP §2143.

If the Examiner resolves the *Graham* factual inquiries, then the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 sets forth the rationales that were established in *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Applicants respectfully submit that the Examiner has not appropriately resolved the *Graham* factors, including the factors of determining the scope and content of the prior art and ascertaining the differences between the prior art and the claims that are at issue. Based on the following, Applicants maintain that the above mentioned *Graham* factors actually reside in Applicants' favor. Additionally, Applicants submit that since the Examiner did not resolve the *Graham* factors, the rationale the Examiner provides for combining the cited references is improper.

Applicants respectfully submit that the present invention is distinct from the cited references and that the Examiner is basing the Examiner's assertions on hindsight reconstruction.

As indicated above, Applicants herein enclose a 37 C.F.R. § 1.132 Declaration of Dr. Brian Frøstrup (as indicated, an executed Declaration will be submitted upon receipt from Applicants). Dr. Frøstrup provides evidence that based on the enclosed data, when compared to the citrate salt of Scheel-Kruger *et al.*, the salt of the present invention shows an unexpected substantial improvement in hygroscopic properties. The DSV sorption profile for the citrate salt shows the citrate salt to be hygroscopic. The mass increase at ambient relative humidity indicates the formation of a monohydrate. Additionally, when comparing the present invention to the citrate salt, for cycle 1, there is a near 20% improvement in mass change at high relative humidity. At decreasing humidity there is still a baseline improvement of 5% change in mass. Also indicated is a near 15% improvement in mass change for cycle 2 at high relative humidity and the same baseline improvement of 5% change in mass.

As indicated, the non-hygroscopic nature of the tartrate salt is important for any commercial use. Scheel-Kruger *et al.* do not teach or suggest that the tartrate salt would

possess any such special properties. The data provided shows that the unexpected substantial improvement in hygroscopic properties of the tartrate salt is an unexpected advantageous result.

Applicants respectfully submit that it is unlikely that the inventive structure of the present invention can be derived, suggested or motivated from the teachings of the '079 patent and Berge reference. Applicants also respectfully disagree with the Examiner that the present invention would be obvious to the skilled artisan based on the teachings of the above cited references.

Due the unpredictability in the chemical arts, the particularly unique structure of the present invention, Applicants respectfully submit that the present invention is not obvious in light of the '079 patent and Berge reference and that the Examiner is applying hindsight reconstruction.

Applicants also bring to the Examiner's attention the positive International Preliminary Report on Patentability (IPRP), which is attached to Dr. Frøstrup's Declaration as Exhibit A. For further clarification, Applicants bring to the Examiner's attention that Scheel-Kruger *et al.*, US Patent No. 6,288,079 B1 is the U.S. equivalent to WO 97/30997.

The IPRP discussed the data presented within the Declaration and is reproduced, in part, below.

1) Reference is made to the following document:

D1: WO 97/30997 A (NEUROSEARCH AS ; SCHEEL KRUEGER JOERGEN (DK); MOLDT PETER (DK); WAETJE) 28 August 1997 (1997-08-28)

2) The present application relates to (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate salts and their use as monoamine neurotransmitter re-uptake inhibitors.

3) Re Item V

3.1 Novelty (Art. 33(2) PCT)

None of the cited documents discloses the particular compound (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate. The claimed subject-matter is therefore regarded as novel.

3.2 Inventive Step (Art. 33(3) PCT)

D1 is considered to be the closest state of the art. This document relates (cf. abstract and pg. 1, par. 1) to the preparation of particular tropane derivatives and their use as monoamine neurotransmitter re-uptake inhibitors in the treatment of disorders such as Parkinson's disease, depression, obsessive compulsive disorders, panic disorders, dementia, etc. For the preparation of the medicinal compositions, ***D1*** *suggests (cf. pg. 7, par. 1) as pharmaceutically acceptable salts a list of acid addition salts comprising* ***tartrate****. It is also mentioned (cf. pg. 8, par. 6), that the resolution of racemic mixtures may be carried out by fractional crystallization of D- or* ***L-tartrates****, mandelates, or camphorsulphonates. Example 15 of D1 discloses the preparation of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane and its* ***citrate*** *salt.*

The subject-matter of the application differs from ***D1*** *in that the compound involved is a* ***tartrate*** *and not to a citrate. The Applicant has shown by means of comparative examples (filed on 19.03.2005) that the tartrate of the invention shows much better properties as regards hygroscopicity than its homologous citrate salt. The problem to be solved by the present application may thus be*

regarded as providing ***less hygroscopic*** *salts of (1R,2R,3S,5S)-2-methoxyMethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane.*

Even though ***D1*** *mentions (see paragraphs indicated above) tartrates among the suitable pharmaceutical salts, this document is silent as to the hygroscopic properties of the resulting substances. Thus, there is no motivation in* ***D1*** *for the skilled person to particularly select tartrates among other pharmaceutically acceptable salts. As this selection is accompanied by an unexpected effect (drastically low hygroscopic character) the claimed subject-matter involves an inventive step.* (Emphasis in original). IPRP for PCT/EP2004/051651.

The courts since *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), have recognized that inventors face additional barriers in relatively unpredictable technological areas as noted in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, *supra* (since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish *prima facie* obviousness of new compound).

Applicants submit that obviousness can not be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (*i.e.* a lead compound) into a particular salt form since the '079 patent and Berge reference do not disclose, teach or suggest that the tartrate salt would possess any such special properties, especially non-hygroscopic properties of the tartrate salt which is important for any commercial use, as in the present invention. Indeed, the data provided within the submitted

Declaration shows that the unexpected substantial improvement in hygroscopic properties of the tartrate salt is an unexpected advantageous result.

Since the '079 patent and Berge reference do not specifically disclose the unexpected advantageous non-hygroscopic properties of the tartrate salt of the instant application, a chemist would not be motivated to modify the compounds of the '079 patent via the Berge reference to make the present invention.

In light of the above remarks, because there is no disclosure, teaching, suggestion, reason or rationale provided in the ''079 patent and Berge reference that would allow one of ordinary skill in the art to arrive at the instant invention as claimed, it follows that the same references are incapable of rendering the instant invention obvious under the provisions of 35 USC § 103(a). Based upon the above, and applying the *Graham factors* analysis test, it is submitted that a *prima facie* case of obviousness has not been established.

Applicants respectfully request reconsideration and subsequent withdrawal of the above rejection.

In view of the above remarks, Applicants believe the pending application is in condition for allowance.

CONCLUSION

A full and complete response has been made to all issues as cited in the Office Action. Applicants have taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicants respectfully request that a timely Notice of Allowance issue for the present case.

In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters within the present application that need to be resolved, the Examiner is respectfully requested to contact Paul D. Pyla, Reg. No. 59,228, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.147; particularly, extension of time fees.

Dated: OCT 10 2008

Respectfully submitted,

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Attachments: 37 C.F.R. § 1.132 Declaration of Dr. Brian Frøstrup